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Dual-acting hybrid drug could be a promising new weapon against drug-resistant malaria

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A combination of artemisinin and another drug (artemisinin combination therapy, ACT) is currently the best malaria treatment recommended by the World Health Organization. In early 2015, artemisinin-resistant malaria was confirmed in five countries in Southeast Asia: Cambodia, Laos, Myanmar, Thailand, and Vietnam. Even more worrying, malaria cases that are resistant to practically all drugs have begun to emerge along the Thailand-Cambodia border. Such cases do not respond to ACT; thus, new therapies that are effective for resistant malaria are urgently needed.

For a therapy to be effective, it needs to counteract the resistance of malaria to existing drugs. Malaria drugs, such as chloroquine and artemisinin, work within the digestive vacuole of the malaria parasite, which serves as the stomach of the parasite. The killing action of chloroquine is better understood than that for artemisinin. Once chloroquine enters the parasite's "stomach," the stomach membrane traps the drug inside (similar to a window closing and locking) and the high levels of drug can then effectively kill the parasite. However, in a resistant malaria parasite, the stomach membrane is mutated so that it cannot keep the drug inside the stomach, just like a window with a broken lock. Since the drug is no longer concentrated inside the stomach, it can no longer kill the malaria parasite effectively.

Associate Professor Kevin Tan of the Department of Microbiology & Immunology and Associate Professor Brian Dymock of the Drug Development Unit and the Department of Pharmacy have now developed a hybrid drug that combines parts of chloroquine and a chemoreversal agent. This gives the hybrid drug a "dual acting" mechanism: a killing factor (chloroquine-derived) and a second component that acts on that faulty window of the parasite's stomach so it can now close again (the chemoreversal agent). The drug becomes concentrated inside the stomach of the drug-resistant parasite and can kill the parasite.

The new hybrid drug killed malaria strains grown in the laboratory as well as malaria parasites from patients in Thailand. Importantly, the drug was very effective against malaria that was resistant to both chloroquine and artemisinin. It was three times more effective than chloroquine at killing these resistant strains. The researchers are continuing to refine the hybrid drug to make it an even more effective therapy for resistant malaria. This work was published online on March 7, 2016 in the journal *Antimicrobial Agents and Chemotherapy*.

Although malaria drugs and chemoreversal agents have been used to treat drug-resistant malaria before, this is the first time that a hybrid of chloroquine and a newly discovered chemoreversal factor has been used in a single novel molecule for this purpose. A single therapy has several advantages that make it a promising new weapon against drug-resistant malaria. Besides being more convenient to take, it has less risk of drug-drug interactions, may be better absorbed and distributed in the body, and could result in slower development of new resistant strains of malaria.

Source:

National University of Singapore
